PB90-112822

Extrapolation Modeling: Advancements and Research Issues in Lung Dosimetry

Duke Univ., Durham, NC

Prepared for:

Health Effects Research Lab., Research Triangle Park, NC

1989

U.S. Department of Commerce
National Technical Information Service
NTIS

PREFACE

Many of the environmental pollutants to which humans are exposed are increasing rapidly, in terms of number, complexity, and concentration. One of the great challenges in environmental medicine is to define more accurately the adverse health effects likely to be encountered by exposures to these pollutants, since reducing exposure to zero is not politically and economically achievable. For many common pollutants, accurate extrapolations from animal toxicology studies to humans and from short-term to long-term chronic effects are essential. The problems that need to be addressed are extremely important, not only to the academic and medical communities which discuss and treat the toxicological problems, but also to governmental agencies which must set regulatory standards, to industry whose products and manufacturing processes contribute to many of the problems, and to the general population which enjoys the benefit of a highly urbanized society but must directly or indirectly pay the health and economic costs associated with either tolerating or removing the environmental pollutants.

The Center for Extrapolation Modeling at Duke University was established in 1986 to coordinate research efforts directed at refining models that more accurately allow data, with respect to dose distribution, injury distribution, magnitude of injury, and patterns of repair, to be extrapolated from one animal species to another. Extrapolation models which can be verified and have characteristics that can be generalized across classes of pollutants offer the only feasible approach for obtaining the data needed to assess effects of the large number of pollutants in our environment. Physical testing of the acute and chronic effects in multiple animal species for large numbers of different pollutants is not an economically realistic approach.

This conference has focused on oxidant air pollutants and modeling of the respiratory system. These are areas in which some of the most extensive data bases exist in the relatively young field of extrapolation modeling. The successful development of effective new models requires a combined input from creative investigators in a broad number of fields. One of the primary purposes of this conference was to assemble these types of investigators in a forum that could focus future research efforts in areas of common interest and facilitate the development and testing of better extrapolation models.

We greatly appreciate contributions from those who participated in the conference and who prepared the resulting manuscripts, all of which have undergone peer review and appear in this monograph. We also appreciate the broad support for this conference which was provided by private industry, academic institutions, and the United States Environmental Protection Agency.

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TECHNICAL REPORT DATA

(Please read Instructions on the reverse before complet

1. REPORT NO.	2.	3.
EPA/600/D-89/143		PB90-112622

4. TITLE AND SUBTITLE
Extrapolation Modeling: Advancements and Research Issues in Lung Dosimetry

5. REPORT DATE

6. PERFORMING ORGANIZATION CODE

7. AUTHOR(S)
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8. PERFORMING ORGANIZATION REPORT NO.

9. PERFORMING ORGANIZATION NAME AND ADDRESS
Center for Extrapolation Modeling
Duke University
Durham, North Carolina

10. PROGRAM ELEMENT NO.

11. CONTRACT/GRANT NO.
CR 813113

12. SPONSORING AGENCY NAME AND ADDRESS
Health Effects Research Laboratory - RTP, NC
Office of Research and Development
US Environmental Protection Agency
Research Triangle Park, N.C. 27711

13. TYPE OF REPORT AND PERIOD COVERED

14. SPONSORING AGENCY CODE
EPA/600/11

15. SUPPLEMENTARY NOTES Proceedings of Extrapolation of Dosimetric Relationships for Inhaled Particles and Gases, J.D. Crapo, J.A. Graham, F.J. Miller, A.W. Hayes, Editors Academic Press, In Press 1989

16. ABSTRACT

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

18. DISTRIBUTION STATEMENT	19. SECURITY CLASS (This Report)	21. NO. OF PAGES 83
	20. SECURITY CLASS (This page)	22. PRICE

EPA Form 2220-1 (Rev. 4-77) PREVIO... EDITION IS OBSOLETE

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EXTRAPOLATION MODELING:
ADVANCEMENTS AND RESEARCH ISSUES IN LUNG DOSIMETRY

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Key Words: dosimetry; lung; toxicity; risk characterization; extrapolation

Disclaimer: The research described in this article has been reviewed by the Health Effects Research Laboratory, U.S. Environmental Protection Agency, and approved for publication. Approval does not signify that the contents necessarily reflect the views and policies of the Agency nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

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I. GOALS OF EXTRAPOLATION MODELING

One of the dilemmas currently encountered when evaluating health effects due to environmental toxicant exposure is a lack of sufficient information on which to base quantitative assessments. Most data on exposures and subsequent effects are available from animal toxicology studies, and more limited data are available from human clinical and epidemiological studies. Though animal toxicology studies provide an extensive base of information, the data are generally used only qualitatively to assess potential health effects in humans. Controlled human exposure studies provide the best information for potential effects, however, ethical considerations prohibit exposures to toxicants under conditions that might elicit a strong response or require highly invasive measurement procedures for assessment of effects. Extrapolation modeling provides a mechanism for combining information from human and animal exposures into an overall assessment of toxicity, thereby taking advantage of the strengths of both approaches while diminishing limitations. Relationships between effects that are known through scientific studies must be used to predict effects that are not known and for which data cannot be accumulated. Specifically, this involves developing experimental correlations between the known acute effects in man and animals as well as between the acute and chronic effects in animals. These relationships can then be used to extrapolate from acute effects in man to chronic effects in man and from chronic effects in animals to chronic effects in man.

To accomplish quantitative extrapolations, three major categories of information are required: dosimetry, species sensitivity, and health effects. Dosimetry refers to the amount of a pollutant which reaches specific target sites after exposure to a given concentration of the pollutant. Species sensitivity refers to potential variations in response of different species receiving the same dose of a pollutant. The linking of dosimetry and sensitivity data allows the quantitative extrapolation of effective pollutant

concentrations between animals and man. To complete the extrapolation, however, the health effects being considered must be adequately understood.

The accumulation of all data required for completing a quantitative extrapolation is a massive undertaking that can be accomplished only with a carefully planned multidisciplinary approach. The intent of this paper is not to address all issues related to extrapolation modeling, but is, rather, to focus on the specific issue of lung dosimetry and provide an overview of accomplishments and goals in this area. Some specific aspects of lung dosimetry to be discussed here are factors affecting dosimetric relationships, methods for determining lung dose, and approaches for modeling or estimating dose.

II. RECENT ACCOMPLISHMENTS

For quantitative extrapolation modeling to become a reality, goals must be clearly defined to ensure the coordination of research projects. Prior to the identification of issues to be addressed, the base of information currently available must be assessed. Much progress has been made in obtaining information required for examining interspecies dosimetry of inhaled compounds, particularly in the areas of physiological variables needed as model input parameters (U.S.E.P.A., 1988) and anatomical structure of the lungs of animals and humans (Mercer et al., 1987; Mortensen et al., 1988). In addition, new data are available on the influence of airway size as a function of age, both from a dosimetry viewpoint (Phalen et al., 1985; Phalen and Oldham, 1987) and relative to a basic understanding of lung growth (Mortensen et al., 1988). Research on quantitating mucous layer thickness for animals and humans within specific regions of the respiratory tract is in progress by Dr. Robert Mercer and colleagues at the Duke University Center for Extrapolation Modeling. Dr. Pi-Wan Cheng and colleagues at the University of North Carolina at Chapel Hill are developing microtechniques to collect mucus for quantitation in animals and humans within specific regions of the respiratory

tract. Also, a new methodology, the aerosol bolus technique (Stahlhofen et al., 1988), offers promise in understanding lung function in individuals with chronic lung disease.

Progress is being made on validating models, however, further refinements of technological approaches which may be useful in model validation, such as isotope ratio mass spectroscopy (Hatch and Aissa, 1987) and positron emission tomography (Coleman et al., 1988), are needed. Examples of recent progress towards model validation are the measurement of total respiratory tract uptake of ozone in various animal species (Wiester et al., 1988) and the determination of regional respiratory tract uptake of ozone in human subjects (Gerrity et al., 1988).

Though dosimetry models for mixtures of gases and particles are not currently available, specific aspects relative to the development of such models have been addressed. Progress to date includes research on individual variations in dose and species (e.g., age dependency) (Phalen et al., 1985, Martonen et al., 1988a and 1988b). In addition, models are available to investigate cellular dose distribution within a given airway (Overton, 1988). Since most situations of actual exposures involve mixtures, development of theoretical constructs is essential for advancement in this area.

A focus of current research is, and should continue to be, identification of the portion of the respiratory tract in which the greatest effect of an inhaled toxicant is seen. The respiratory tract serves as the portal of entry for many environmental pollutants. Since the pollutant is continuously removed from the inhaled airstream, the concentration in the lumen of lung airways declines distally from the trachea. Simultaneously, the liquid layer lining the tracheobronchial airways that protects underlying tissue decreases in thickness and may undergo changes in composition. Thus, the pattern of cellular injury is often seen more distally in the airways, as with the case of ozone (Figure 1). For many inhaled toxicants, such as the oxidant gases, the site of greatest lung injury occurs near the bronchiole-alveolar duct (BAD) junction (Barry et al., 1985; Chang et al., 1986 and 1988). The point of maximal effect, however,

can vary with different compounds. Specifically, the area of maximal effect is likely to depend upon the nature of the toxicant and its effect, as well as the organ in which toxicity is observed. The accomplishments described in later chapters reflect procedures which apply to multiple endpoints and organs and can help identify regions of maximal effect. An integration of multifaceted data will advance the understanding of environmental contaminant toxicity and further the goals of quantitative extrapolation modeling.

III. INTERDISCIPLINARY SYNTHESIS OF CONCEPTS AND KNOWLEDGE

To estimate human toxicity from exposure to chemicals and to characterize risk from these exposures, an interdisciplinary synthesis of concepts and knowledge is essential. The process for achieving these goals involves several components (Figure 2). One component is development of a data base of basic information regarding exposures and effects reported in the literature (e.g., the Critical Toxicity Reference System (Smolko et al., 1986)). Another component involves using the information system to compile data regarding anatomical, physiological, biochemical, and physical parameters for species of interest. Such accumulated information can then be used to develop physiologically-based dosimetry models for predicting dose to specific target sites. Dose-response relationships are established by correlating dose (from physiologically-based dosimetry models and reported exposure regimens) with effects resulting from the exposure regimens. Such relationships from animal studies may require translation to expected dose-response patterns for humans. The sensitivity of a particular species to effects of interest must also be factored into the analyses. This type of algorithm allows the estimation of human toxicity when sufficient data are available.

Alternatively, when sufficient data are not available, the process shown in Figure 2 can be used to identify research gaps and design appropriate experiments to address the needs. As exemplified by the research projects that have been enacted relative to

nasopharyngeal removal of ozone in man and laboratory animals, interdisciplinary research is critical for filling data gaps and for furthering quantitative extrapolation modeling. Physiologically-based dosimetry models have been developed for predicting the lower respiratory tract uptake of ozone in man (Miller et al., 1985) and in the rat (Overton et al., 1987), however, these dosimetry models require that the ozone concentration just above the trachea be specified. Several years ago, such data were not available.

Interactions among scientists regarding animal and human physiology, animal and human morphometry, aerobiology, physics, biochemistry, analytical chemistry, electrical engineering, inhalation engineering, and biostatistics were necessary to obtain the nasopharyngeal removal data. While this undertaking was extremely complex, some major accomplishments evolved from these scientific interactions. Research activities included: 1) modifying an ozone analyzer to achieve a sufficiently rapid response time for breath-by-breath measurements in human subjects; 2) performing concentration-response studies in human subjects and developing a method to deconvolute the signal from instrumentation used to measure uptake; 3) developing an exposure system which minimizes dead space and allows mass balance expressions to include adjustments for lag-time responsiveness of the instrumentation; 4) developing an improved restraining system for exposure of rats in a sensitive mass balance exposure apparatus; and 5) applying isotope-ratio mass spectroscopy in biochemical studies to determine the relative proportionality of $^{18}O_3$ removed in the heads of rats and using these findings to adjust total respiratory tract uptake data obtained in the mass balance studies for estimates of nasopharyngeal uptake. Experimental factors (e.g., protocols, techniques) had to be coordinated among scientists to ensure data comparability and utility for input into ozone dosimetry models. As a result of these efforts, the original data base has been expanded, and the dosimetry models can be used to improve characterization of human risk from exposure to ozone. While this procedural application has focused on

ozone, the principles involved relate to extrapolation modeling of inhaled chemicals, in general.

IV. FUTURE DIRECTIONS

One of the major issues to be addressed over the next several years relative to extrapolation models concerns validation. A model can be most useful to predict across different species and exposure scenarios if its accuracy and limitations are known. Model validation has been an extremely difficult task to achieve for some of the reactive gases. Since the data set used to develop a model should not be used to test the validity of that model, new data are needed for the validation process. The utilization of new experimental methodologies can have a significant impact on model validation, however, a greater and continued effort is required in many areas.

Comparative biology is one area which should receive special emphasis. The incorporation into models of actual biological values, rather than "best estimates", would contribute significantly to the utility of these models. In addition, an enhanced understanding of the quantitative differences between various animal species and man will improve judgments related to defining the most appropriate species to be used for studies, understanding limitations of available data, and synthesizing information across experimental studies of different designs. The American Review of Respiratory Disease (Volume 128, Number 2, 1983) is an excellent resource for the types of comparative biological data which affect interspecies judgments on effects of inhaled material on respiratory tract issues. This journal supplement is based on a 1982 workshop on the comparative biology of the lung sponsored by the National Heart, Lung, and Blood Institute of the National Institutes of Health. Continued research in this area is essential for the development and refinement of extrapolation models.

Another major research issue is to determine whether or not subgroups that are especially susceptible to the effects of exposure to particular environmental pollutants

exist within the general population. The majority of information currently available relates exposure and effect to the normal population, with some emphasis within this normal population on effects in children, exercising adults, or individuals with pre-existing disease (U.S.E.P.A., 1982 and 1986a). Some data showing deposition of particles relative to various disease states have also been generated (Stahlhofen et al., 1988), however, much of the morphological data that would provide input for model construction are not available. Groups that should be studied further include, but are not limited to, individuals with chronic bronchitis or emphysema and smokers. Though some limited data on deposition of particles in smokers are available (Lippmann et al., 1971; Lippmann, 1977), specific information on changes in lung structure and function that will affect pollutant gas distributions in the lungs of individuals within this large subgroup are not available. The susceptibility of any population subgroup must be given particular consideration when assessing environmental effects.

Studies on the clearance of inhaled pollutants from the lung are also needed. Information on initial dose deposition is available (U.S.E.P.A., 1982 and 1986b); however, retained dose, which factors in the temporal pattern of uncleared pollutant, is more relevant when examining long-term effects. The net bioavailability of gases or particles is inextricably associated with these resulting effects. Moreover, the dosimetry of hygroscopic particles will continue to be an evolving and important field of investigation, since acid aerosols are recognized as major constituents of environmental pollution.

A great deal of current research relates to issues of species sensitivity and toxicodynamics. As mentioned previously, species sensitivity refers to the dose delivered to a target site which generates an equivalent biological response. This factor is becoming increasingly important as research progresses towards a quantification of species differences essential for extrapolation modeling. Also, microdosimetric information is desirable if toxicological assessments are to be focused on very specific

anatomical locations within the respiratory tract. Additional data on mechanisms and structure will allow identification of localized target areas to be examined for critical effects. This should lead to improved decisions regarding intraspecies versus interspecies effects, various risk assessments, and applicable uncertainty factors. Without knowledge of the basic biochemical and molecular alterations leading to an effect, unfocused studies could generate data on effects and/or species that are vastly different and unrelated.

Studies on mechanisms should focus on determination of whether similar mechanisms of toxicity are operative at both high concentration and low concentration exposures. For example, the overloading of clearance mechanisms may cause cumulative dose effects with high exposure levels that do not occur with low levels of exposure (Morrow, 1988). The implication is that effects associated with these high exposure levels may not be the same as those observed in more realistic human exposures, or at least that they cannot be linearly extrapolated. Since the goal is defining human risk, high to low dose extrapolation issues must be addressed.

If appropriate models for extrapolation are to be developed, their particular application must be clearly defined. The problem could be defined as the need to establish a National Ambient Air Quality Standard for a ubiquitous pollutant or to control point source emissions. The specific nature of each scenario will determine the analytical aproach to be used and the emphasis to be placed on model validation.

Further, the ultimate goal of defining human risk must be a common theme in all extrapolation modeling efforts. Without coordinated research, many studies are likely to be performed that may not optimally contribute to efforts toward reaching the common goal. Individuals with various areas of expertise must work together as a team to improve the data base on animal and human differences that relate to anatomical, physiological, and biochemical effects or parameters that modulate dose. Basically, this constitutes development of physiologically-based dosimetry models. Dosimetric models

are used to synthesize information and to integrate concentration-response and exposure relationships, leading to estimations of human toxicity. Concentration-response information from animals and humans can be translated into dose-response information associated with target sites of interest for specific effects. However, dose can have different connotations, depending upon the effect being studied. Different dose measures (e.g., surface area, number of particles, number of fibers, total mass) may be appropriate for estimation of different toxic effects.

Extrapolation modeling involves conceptual processes that identify research gaps and facilitate the design of experiments to broaden the base of information for risk assessments. Research described in subsequent chapters contributes toward improved human risk characterizations. Specific issues in the area of dosimetry of inhaled particles and gases which will be addressed include: lung structure/function relationships that influence distribution; experimental dosimetry; new methods for determining dosimetry; and modeling approaches for predicting dosimetry. Though the data presented contribute substantially to the extrapolation effort, additional work is needed to understand fully the relationships between exposures to environmental pollutants and the resulting effects.

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VI. FIGURE LEGENDS

Figure 1. Lung injury by inhaled oxidants. The BAD junction is the bronchiole-alveolar duct junction, a site at which a number of inhaled pollutants have been shown to exhibit their maximal toxic effects.

Figure 2. Process for synthesizing interdisciplinary concepts and knowledge to characterize human risk from exposure to toxicants (adapted from Miller et al., 1987).

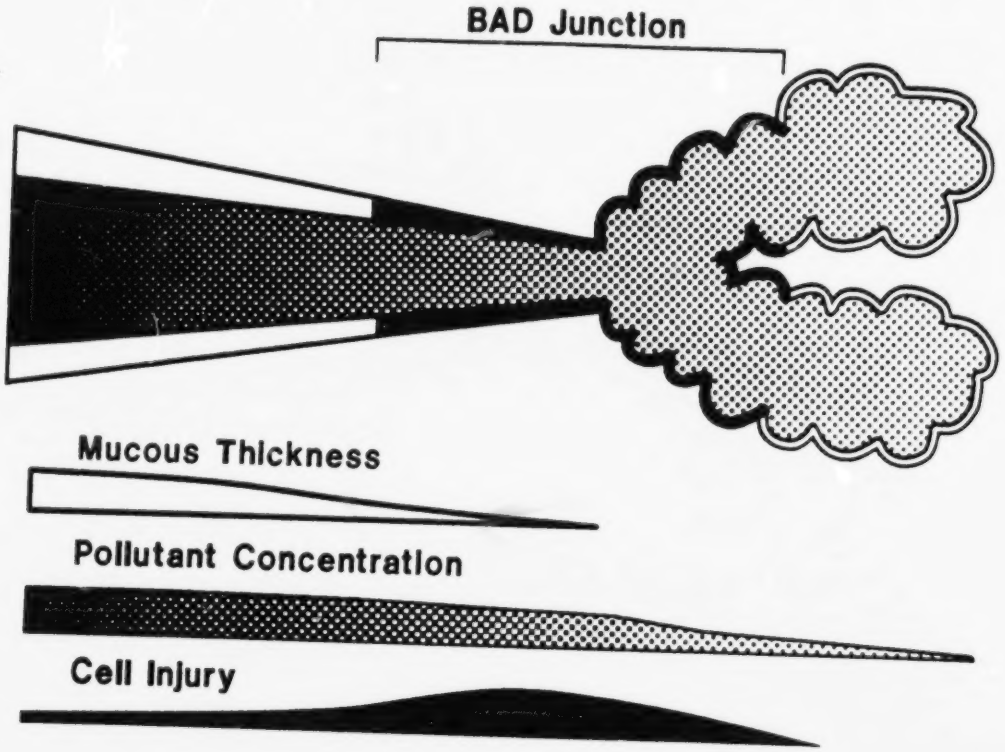
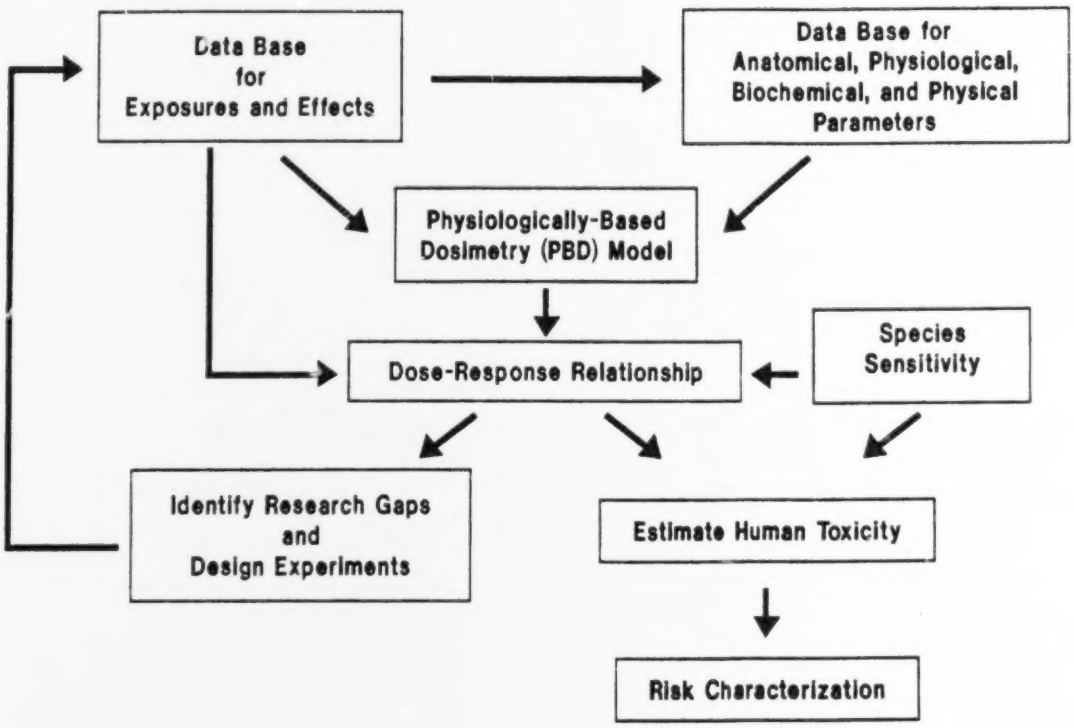

BAD Junction
Mucous Thickness
Pollutant Concentration
Cell Injury

Figure 1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Dose-Response Relationship
Identify Research Gaps
and
Design Experiments
Estimate Human Toxicity
Risk Characterization

Figure 2